PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference AH/P89548PWO	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/GB2005/000151	International filing date *(day/month/year)* 17 January 2005 (17.01.2005)	Priority date *(day/month/year)* 17 January 2004 (17.01.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant THE UNIVERSITY OF MANCHESTER		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 12 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 27 July 2006 (27.07.2006)
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Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2005/000151	17.01.2005	17.01.2004

International Patent Classification (IPC) or both national classification and IPC
INV. A61K47/48

Applicant
THE UNIVERSITY OF MANCHESTER

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2005/000151

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 28-39

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 38-39 are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 28-39

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-27

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-27
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-27
Industrial applicability (IA)	Yes:	Claims	1-27
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1 Reference is made to the following documents:

D1: Nakamura M et al: "Stereochemistry and Total Synthesis of Dolastatin E" TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 36, no. 28, 10 July 1995 (1995-07-10), pages 5059-5062, XP004027736 ISSN: 0040-4039

D2: MCKEEVER B et al: "Total synthesis of the prenylated cyclopeptide trunkamide A, a cytotoxic metabolite from Lissoclinum sp" TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 42, no. 13, 26 March 2001 (2001-03-26), pages 2573-2577, XP004232300 ISSN: 0040-4039

D3: LE H-T et al: "Design of potent dynorphin A-(1-9) analogues devoid of supraspinal motor effects in mice" CANADIAN JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY, vol. 75, no. 1, 1997, pages 9-14, XP008060098 ISSN: 0008-4212

D4: CLAUSEN K et al: "STUDIES ON AMINO-ACIDS AND PEPTIDES 6. METHODS FOR INTRODUCING THIOAMIDE BONDS INTO THE PEPTIDE BACKBONE SYNTHESIS OF THE 4 MONOTHIO ANALOGS OF LEUCINE ENKEPHALIN" JOURNAL OF THE CHEMICAL SOCIETY PERKIN TRANSACTIONS I, no. 4, 1984, pages 785-798, XP002369346 ISSN: 0300-922X

D5: LEHMANN J et al: "Synthesis of endothiopeptides and their cyclization to 1,3-thiazol- 5(4H)-imines" HELVETICA CHIMICA ACTA 1999 SWITZERLAND, vol. 82, no. 11, 1999, pages 1899-1915, XP002369347 ISSN: 0018-019X

D6: ZACHARIE B et al: "Thioamides: Synthesis, stability, and immunological activities of thioanalogues of imreg. Preparation of new thioacylating agents using fluorobenzimidazolone derivatives" JOURNAL OF MEDICINAL CHEMISTRY, Vol. 42, no. 11, 3 June 1999 (1999-06-03), pages 2046-2052, XP002369348 ISSN: 0022-2623

D7: LAJOIE G et al: "FACILE REGIOSELECTIVE FORMATION OF THIO PEPTIDE LINKAGES FROM OLIGO PEPTIDES WITH NEW THIONATION REAGENTS" TETRAHEDRON LETTERS, Vol. 24, no. 36, 1983, pages 3815-3818, XP002369349 ISSN: 0040-4039

D8: BROWN D W et al: "MONOTHIONOPEPTIDE AND DITHIONOPEPTIDE SYNTHESIS" TETRAHEDRON LETTERS, Vol. 28, no. 19, 1987, pages 2171-2174,

XP002369350 ISSN: 0040-4039

D9: ZACHARIE B et al: "Thioacylating agents. Use of thiobenzimidazolone derivatives for the preparation of thiotuftsin analogs" TETRAHEDRON, Vol. 49, no. 46, 1993, pages 10489-10500, XP002369351 ISSN: 0040-4020

D10: LA COUR T F M: "STEREOCHEMISTRY OF PEPTIDES CONTAINING A THIOACYL GROUP" INTERNATIONAL JOURNAL OF PEPTIDE AND PROTEIN RESEARCH, vol. 30, no. 4, 1987, pages 564-571, XP008060097 ISSN: 0367-8377

D11: ELMORE D T et al: "Thioesters of amino acid deriviatives as thioacylating agents in thiopeptide synthesis" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, no. 5, May 1988 (1988-05), pages 1051-1055, XP002140044 ISSN: 0300-922X

D12: CAMPBELL P et al: "CARBOXYPEPTIDASE A CATALYZED HYDROLYSIS OF THIOPEPTIDE AND THIONESTER ANALOGUES OF SPECIFIC SUBSTRATES. AN EFFECT ON KAPPACAT FOR PEPTIDE, BUT NOT ESTER, SUBSTRATES" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 104, no. 19, 1982, pages 5221-5226, XP009029516 ISSN: 0002-7863

D13: LEHMANN J et al: "Site-Selective Incorporation of Thioamide-Linkages into a Growing Peptide" TETRAHEDRON, Vol. 55, no. 17, 23 April 1999 (1999-04-23), pages 5359-5376, XP004223048 ISSN: 0040-4020

D14: SHAO Y et al: "Endothiopeptide inhibitors of HIV-1 protease" BIOORGANIC &; MEDICINAL CHEMISTRY LETTERS, vol. 8, no. 6, 17 March 1998 (1998-03-17), pages 699-704, XP004136948 ISSN: 0960-894X

D15: MCKEEVER B et al: "Total synthesis of trunkamide A, a novel thiazoline-based prenylated cyclopeptide metabolite from Lissoclinum sp" TETRAHEDRON, Vol. 59, no. 15, 7 April 2003 (2003-04-07), pages 2713-2727, XP004417708 ISSN: 0040-4020

D16: US 5 457 180 A (ZACHARIE et al) 10 October 1995 (1995-10-10)

D17: WO 91/01976 A (IAF BIOCHEM INTERNATIONAL INC) 21 February 1991 (1991-02-21)

D18: WO 99/20649 A (MERCK PATENT GMBH; NAUMANN, RENATE; JONCZYK,

ALFRED; SCHMIDT, EVA-KATH) 29 April 1999 (1999-04-29)

Re Item III.

Present claims 38 and 39 do not define the scope of protection sought in technical terms, contrary to the requirement of Article 6 PCT, and can therefore not be searched nor be properly compared to any prior art.

Re Item IV.

The separate inventions/groups of inventions are:

No.	Claims	Subject
1	1-27	A thiopeptide according to these claims
2	28-33,36-37	A drug conjugate according to these claims, and its use in a method of treatment.
3	34-35	An assay to detect transportation of a conjugate across a membrane.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The problem underlying the present application is to provide new transmembrane drugs.
As solution to this problem, the drug is conjugated to a thiopeptide.
The thiopeptides themselves are claimed separately. They solve a different problem: to provide new drug carriers.
Finally, an assay for determining if a conjugate crosses a membrane is also claimed. This assay solved the problem of how to determine the transmembranary efficacy of a substance.
The technical feature linking a priori these subjects together is the thiopeptide.

However, thiopeptides have already been described in the prior art.
Document **D1** discloses a thiopeptide having Ala-CS-Ser at the COOH side. This

thiopeptide forms a thiazole. In the present application, thiopeptides containing CS-Ser at the COOH side are preferred.
Document **D2** discloses a thiopeptide having a serine residue at the COOH side. In the present application, thiopeptides containing CS-Ser at the COOH side are preferred.

The present application also indicates, that thiopeptides more easily cross membranes. This technical aspect of the present application is, however, also known from the prior art: Document **D3** discloses the preparation of the thiononapeptide dynorphine. Its cerebral effects, i.e., after passing the blood-brain-barrier, are determined.

Therefore, these technical features can no longer serve as special technical feature in the sense of Rule 13 PCT, linking the different subjects together.
Since there is no other technical feature, that could fulfil the role of special technical feature in the sense of Rule 13 PCT, the present application lacks unity of invention, containing the subject-matters as listed.
In principle, each of the compounds mentioned in the claims represents a different invention. However, in order to reduce the number of subjects as much as possible, the compounds have been regrouped according to structural similarities.
Although some document cited in the present search report may also be pertinent for further inventions mentioned this does not imply, that the search for those subjects has been fully performed.
As searching the other inventions and establishing the Written Opinion of the International Search Authority (WO-ISA) requires more than only "negligible additional work", the search and Written Opinion have been restricted to the first invention only, see also the PCT International Search and Preliminary Examination Guidelines, 10.65.

Re Item V.

Invention 1

Document **D1** discloses a thiopeptide having Ala-CS-Ser at the COOH side. This thiopeptide forms a thiazole. In the present application, thiopeptides containing CS-Ser at the COOH side are preferred.

Document **D2** discloses a thiopeptide having a serine residue at the COOH side. In the present application, thiopeptides containing CS-Ser at the COOH side are preferred. Document **D3** discloses the preparation of the thiononapeptide dynorphine. Its cerebral effects, i.e., after passing the blood-brain-barrier, are determined.

Documents **D4** to **D17** also describe several thiopeptides and their synthesis. In **D7** and **D9**, di- to pentapeptides are prepared. In **D8**, tetrapeptides are prepared. **D10** discloses the preparation of six thiopeptides. **D11** discloses several compounds containing a group of the formula NH-CH_2-(C=S)-NH-CH_2-COOH : $PhCH_2O$(CO)NH-CH_2-(C=S)-NH-CH_2-COOH, $PhCH_2O$(CO)NH-CH_2-(C=S)-NH-CH_2-(CO)-NH-CH_2-COOH, etc. **D12** discloses compounds containing different groups attached to the amine end of formulae I et II. These compounds nevertheless oppose to the novelty of present claims 1-7. **D14** discloses several endothiopeptides which inhibit HIV1-protease.

In view of these documents, the presently claimed thiopeptides do not meet the requirements of Article 33.2 PCT for novelty.

This lack of novelty is not overcome by the fact, that the existing thiopeptides now seem to solve a different problem. Indeed, the characteristic of being more resistant to hydrolysis has not been an invention of the present application, but rather an inherent property of the thiopeptides.

Also, the derivatisation of the peptide in order to become a drug carrier takes place, according to page 26 of the present application, at a serine residue at the COOH side of the thiopeptide. Therefore, a thiopeptide *adapted to carry or transport a drug* as required by claim 1 is in fact very specifically anticipated by both **D1** and **D2**.

On the other hand, several thiodipeptides have been disclosed in documents **D4** to **D17**. Therefore, even the thiopeptides according to formula (II) seem to be anticipated.

Insofar as certain specific thiopeptides are not anticipated, they do not seem to fulfil the requirements of Article 33.3 PCT for inventive step. The problem to be solved by such specific thiopeptides would be to provide a carrier molecule for transport of drugs across membranes. However, this improved transmembrane activity has already been described

for thiopeptides in **D3**, in which a thiopeptide is compared to its "normal" peptidic analogue. In this document, the membrane is the blood-brain barrier.
Like in the present application's examples, the transmembrane transport is determined only for the non-conjugated (thio)peptide.
Therefore, the present application does not seem to go beyond the disclosure of **D3**.

Re Item VIII.

Present claims 38 and 39 do not define the scope of protection sought in technical terms, contrary to the requirement of Article 6 PCT.
As is clear from **D18**, the expression "thiopeptide" is equivocal. Therefore all claims mentioning this expression are also equivocal, contrary to the requirement of Article 6 PCT.
Due to the expressions "derivative or analogue thereof", "functional group", "adapted to carry or transport a drug", the claims do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.